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CHILDREN'S HOSPITAL

OF THE DISTRICT OF COLUMBIA

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Clinical Proceedings

CHILDREN'S HOSPITAL WASHINGTON, D.C.

VOLUME XVII • JUNE 1961 • NUMBER 6

SYMPOSIUM: TOTAL BODY IRRADIATION*

INTRODUCTION

LIEUTENANT DAVID HARRIS, MC, U. S. N.†

On Monday, January 26, 1896, in the faculty room of one of the medical colleges of Chicago, Illinois, a member of the faculty was examining the hand of one of the medical students. This student was Dr. Emil Grube. Grube, in addition to being a student of medicine, was also an instructor in chemistry and physics, and since 1895 had been involved in the manufacture of Crookes's tubes. His left hand showed evidence of a severe dermatitis, looking as though it had been scalded, and was swollen to twice its normal size. Grube explained that for almost a year he had placed his left hand between the electrically excited Crookes's tube and the screen of fluorescent crystals to test the vacuum in the tube; many times his hand had been almost in contact with the tube. Several of the physicians present offered suggestions as to how to treat the dermatitis. However, one who was present, Dr. J. E. Gilman, offered no treatment, but, reflecting on the effect of the rays emanating from the Crookes's tubes, was quoted as saying, "Any physical agent capable of doing so much damage to normal or healthy cells in tissues might offer possibilities if used as a therapeutic measure in the treatment of pathologic conditions in which pronounced irritated blistering or even destructive effects might be desirable." Dr. Gilman went so far as to suggest that these rays might be used to treat indolent ulcers and even carcinoma. This was in 1896.

Several of those present were impressed by this idea. Three days later a 55 year old woman with carcinoma of the left breast and severe systemic spread appeared in the laboratory. This woman received 18 hours of exposure to x-radiations emanating from a Crookes's tube positioned three inches from the diseased breast. She experienced some relief of symptoms but unfortunately went on to die of carcinoma.

* Presented by the Department of Pediatrics, U. S. Naval Hospital, Bethesda, Maryland, at the Metropolitan Area Pediatric Conference, January 28, 1960.

† Resident in Pediatrics, U. S. Naval Hospital, Bethesda, Maryland.

It was thus that almost 64 years ago, only three months after the discovery of x-ray by Röentgen in November 1895, and almost a year before the discovery of radioactivity by Becqueral in November 1896, that the concept of treating malignant tumors with ionizing radiation was born. Further, it is curious that it fell to one man, Dr. Emil Grube, to be the first to suffer injury from ionizing radiation and to be the first to use this powerful force therapeutically.

The Biological Effects of Ionizing Radiation

LIEUTENANT GORDON B. AVERY, MC, U. S. N.*

Ionizing radiation is all around us. It bombards us in the form of cosmic rays coming from the vast reaches of space. It emanates from elements in the earth's crust which decay with the release of high energy particles. Radiation from x-rays is made by man for medical use in countless hospitals and doctors' offices. In the laboratory of the physicist, huge machines such as cyclotrons and betatrons are used to create ionizing radiation. Unstable radioisotopes, because of their ionizing radiation, are used in medical and biological research. Lastly, and most spectacularly, ionizing radiation in tremendous quantities is generated by nuclear fission and fusion in atomic piles and in atomic and hydrogen bombs.

There are many rays and particles capable of causing ionizing radiation; all these rays and particles have in common the ability to create ions. An ion is a particle of atomic dimensions carrying an electrical charge. Tens of thousands of ions may be created in the wake of a single high energy particle.

The apparent solidness of matter hides a considerable amount of empty space. The atom may be compared to our solar system, in that the atomic nucleus is an object of relatively large mass similar in some ways to the sun, and the orbital electrons revolve around it like planets. The electrons are negatively charged, and the nucleus has just sufficient positive charge so that the sum of all the charges is zero.

When, for example, a high energy alpha particle passes close to such an atom it exerts an electrical force on the orbital electrons and may tear one loose and send it off on an independent course. The free electron thus becomes a negative ion and the disrupted atom, now with a net positive

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charge, becomes a positive ion. These ions are relatively unstable and enter readily into chemical reactions.

Alpha rays and beta rays are subatomic particles accelerated to very high energies. X-rays and gamma rays are units of electromagnetic radiation similar to light or radio waves except for their very high energy. What distinguishes them from ordinary light is the fact that they can, by impinging on particles of air or matter, create ions. In either case, it is ions which mediate the biological effect of radiation.

A gamma ray has no charge and therefore must come into the immediate vicinity of an atom to disrupt its electrons. In contrast, a beta particle, because of its charge, exerts an electrical force that can disrupt planetary electrons at some distance from its actual path. Thus, when a beta ray passes through matter, a dense track of ions is created, and in a short distance the energy of the beta ray is completely dissipated. In contrast, a gamma ray passing through the same substance causes a much less dense track of ions and hence passes with only slightly diminished energy through a considerable thickness of matter. The extremes of this phenomenon are illustrated by noncharged cosmic rays, which may pass only partly diminished through several inches of lead, and doubly charged alpha particles, which may be stopped by a sheet of paper.

One protagonist in the drama of ionizing radiation is the radiation itself; the other is the reacting cell. The most characteristic thing about any cell—about life itself—is its orderliness. A seemingly infinite amount of information is required to specify all the parts of a cell, down to the molecular level, and to arrange them all in proper proportions and spatial relationship. Many seemingly minor variations in the cellular apparatus are incompatible with life.

Figure 1 is a stylized picture of a cell, separated into quadrants representing different levels of organization. The grossest kind of structure which cells display is their tissue differentiation. Illustrated in the left upper quadrant is the sort of special structure that a muscle cell has, with its linear striations and special contractile proteins. These structures are relatively insensitive to radiation, probably because the contractile apparatus is duplicated many times over. There are literally billions of actinomyosin molecules, so that if a few are destroyed, there are still many left to perform the functions of the cell. For the most part the functions of a cell related to tissue differentiation are radioresistant. Highly differentiated cells, in general, are more radioresistant than rapidly dividing, undifferentiated stem cells.

The right upper quadrant represents the structure which might be seen in a tissue culture, viewed with a phase microscope. The cell membrane, the nuclear membrane, the inclusion droplets and granules in the cytoplasm

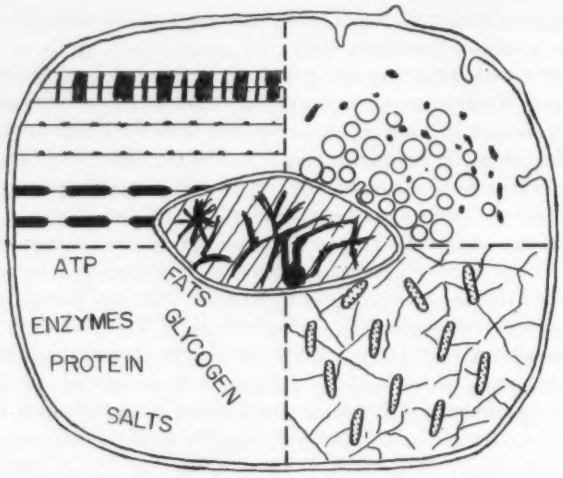

FIG. 1. Stylized drawing of a cell

all represent interfaces at which important interactions occur. These too are relatively radioresistant, apparently because no single locus is crucial to cell function.

The right lower quadrant represents cytoplasmic organelles which are revealed by the electron microscope. The mitochondria and endoplasmic reticulum are now known to possess respiratory and synthetic enzymes arranged in sequential order. However, these too are relatively insensitive to radiation, apparently because these structures are duplicated many times over.

The left lower quadrant represents schematically the molecular soup in which proteins, carbohydrates, enzymes, etc., are free in solution and react only as they chance to collide. The position of molecules in the sol phase is not specified, but the precise configuration within some of the molecules is indeed specific. The mere refolding of some proteins is enough to destroy activity. This can be easily accomplished by radiation, and indeed it is sometimes possible to show a temporary fall in enzyme activity after irradiation. Once again the saving grace is that even the rarest enzymes are present in sufficient numbers of molecules so that they are unlikely to be all simultaneously destroyed.

The nucleus, of course, contains the heart of the matter. Whereas in the cytoplasm there is usually a duplication of structures, in the nucleus there is only one pair of each chromosome, and only a very finite amount of DNA carrying each code unit of heredity. When this is destroyed, the

cell has no way of replacing it. It is therefore not surprising that the nuclei, and in particular the chromosomes, are the most sensitive structures in the cell to low doses of radiation. A wasp egg, for example, irradiated with a single alpha particle which traverses the nucleus, is incapable of growing and dividing. If the cytoplasm is irradiated instead, it requires a million alpha particles to achieve the same effect.

The energy of ionizing irradiation is often so large that a single gamma ray may leave in its wake 100,000 ionizations. The substance ionized is a matter of chance, but often it is water because of the prevalence of water in the cell. Besides simple hydrogen and hydroxyl ions there are produced various free radicals and peroxides which are highly unstable. These in turn may enter into unusual chemical reactions with larger and more sluggish molecules such as proteins or DNA. In general these are oxidizing reactions, and reducing substances have in fact been found to protect against radiation. It is secondary chemical reactions which chiefly mediate the biological effects of ionizing radiation and extend the damage beyond the actual track of one ionizing particle. All the above events usually take place within a millionth of a second, yet the biological effects of this chemical damage may take days or even weeks to be fully expressed.

When a tissue culture, or any other collection of single cells, is irradiated, the effect depends on the dose. A small dose of radiation may cause a lag in mitosis, but thereafter the cells return to normal function. A larger dose may leave some cells unharmed whereas others may fail to divide or may divide and die. Finally, with a sufficient dose, there is immediate massive cell death. This is because with increasing dose there is increasing chance that the irradiation damage within a given cell will destroy a vital structure. When the damage is not lethal, the passage of time allows the cell to repair itself.

Cytologically, one sees changes in the chromosomes of the irradiated cell. Sometimes there are actual breaks in the chromosomes, and fragments are left behind at mitosis. Sometimes the chromosomes become sticky and fail to segregate normally at mitosis. Sometimes the chromosomes break and come back together again, producing bizarre forms. On the molecular level we can imagine that even greater violence is being done to the code units of heredity. It is these changes rather than transient variations in cell permeability and metabolism which are the important biological effects of radiation.

Chemical damage to the hereditary DNA may cause gene mutations. Repaired chromosome breaks may cause disordered gene sequence with functional impairment. Genes are probably the ultimate source of the information from which all other cellular organization is derived. Almost every detail of the enormous DNA molecule is thought to be precisely

specified. It is small wonder that the intrusion of ionizing radiation into this storehouse of essential information is fatal to the cell.

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Experience with Total Body Irradiation Therapy

LIEUTENANT COMMANDER H. A. PEARSON, MC, U. S. N.*

Nuclear power reactors are being increasingly used for both experimental and technical purposes. As long as they are used, the human factor will come into play, resulting in human error. Accordingly, persons may be accidentally exposed to large doses of total body irradiation and physicians will be involved in management and therapy of these victims. How does one in the ordinary scheme of things acquire any experience in treating an individual who has been exposed to large amounts of ionizing radiation? How can any research on the therapy of this condition be undertaken? The answers to this type of problem are offshoots of a program currently in effect at the National Naval Medical Center. We are using total body radiation as a modality for the therapy of selected cases of advanced malignancy and leukemia.

There are theoretical advantages to total body irradiation over local irradiation. Many roentgen therapists have noticed that when a primary neoplasm is irradiated, disappearance of lesions outside the primary x-ray field may be observed. This suggests that there may be some necrotoxin produced by radiation, or some humoral effect upon certain cancers. It is also true that some tumors become disseminated so early in their course that any treatment directed at the tumor, is, in effect, total body treatment. And, finally, a sad-but-true clinical situation which physicians face daily is that patients with malignancies become refractory to conventional therapy.

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At this point, unconventional or unproven treatments may rationally be employed for palliation.

At the National Naval Medical Center we have available a unique unit for total body radiation therapy. This employs 2500 curies of Cobalt^{60}. Co^{60} is a radioactive isotope which emits a powerful monoenergetic gamma ray. The 2500 curies in this apparatus are arranged in two concentric cylinders, approximately 7 feet in length. Radiation physicists term this spatial configuration a 4 π geometry. Within this device, the patient's entire body receives radiation which is almost uniform. There is only a 10 per cent difference between the amount of radiation received by the skin and the center of the body. Because of the large amount of isotope, a very large dose of whole body radiation can be administered over a relatively short period of time. In practice, it is possible to administer as much as 30 r. per minute to a patient.

We have treated a small group of patients using this apparatus. They can be divided into several different clinical groups. The first group consists of 7 patients, 5 adults and 2 children, with terminal disseminated cancer, who were considered moribund and candidates for palliative therapy. One of the children had disseminated Wilms's tumor which had widely metastasized throughout the abdomen and into the chest. The other child had a mesothelioma of the pleura which had invaded the mediastinum and penetrated the diaphragm. These children were both given total doses of 500 r. of whole body radiation in divided doses of 100 r. on alternate days. They tolerated this radiation extremely well; there was no nausea, vomiting, or other signs of radiation sickness. The tumor effects, although temporary, were striking. Within four or five days, a decrease of five inches in abdominal girth occurred in the child with Wilms's tumor. Coincident with this, there was increase in well-being, and the distension of her abdomen with its venous pattern disappeared. Even though she had entered the hospital in what was considered a moribund state, she was well enough to go home for two weeks. The child with mesothelioma, a radio-resistant tumor, also had striking clinical improvement. Her breathing became easier and there was some tumor regression noted by x-ray. Both these children, in addition to previous local x-ray therapy, had received the usual chemotherapeutic agents, including Actinomycin-D and nitrogen mustard.

The hematologic effects of the radiation on these children were striking. Initially there was a brief rise in the peripheral white blood cell and platelet counts, followed by a slow progressive drop. Two weeks after completion of the course of radiation, the children were severely pancytopenic. They had white blood cell counts less than 1,500 and platelet counts under 10,000. Despite this very significant neutropenia and thrombocytopenia, hemorrhage and infection were not problems. No stringent isolation pre-

cautions were used; the children were in private rooms, but their parents were allowed to visit. The child with mesothelioma developed a pneumonitis which responded to conventional doses of penicillin. Hematologic depression persisted for about 30 days, after which a return of the neutrophil count to normal was seen; this was followed a week later by the return of the platelet count toward normal. Consequently, 40 days after the course of irradiation, the white blood cell count was 7,000 per cu. mm. in both children, and the platelet counts were between 100,000 and 125,000.

These children lived for approximately two months after the course of total body irradiation; they died of inanition—essentially, "cancer deaths." It is felt that not only was significant palliation attained, but also some prolongation of life. Total body irradiation administered in this fashion in divided doses therefore did seem to offer definite if temporary palliation for these children with advanced malignancies. It is also important to note that this form of therapy given to a patient with an already depleted marrow was not fatal from a hematologic point of view.

Total body irradiation in the 900 to 1200 r. range produces irreversible damage to the bone marrow. This dose of radiation can probably be considered about the LD 100 for man. Death from this dose is usually delayed and is secondary to hematopoietic failure. Therefore, reasonable chance for recovery depends either on protecting the marrow in some way before exposure or replacing it with normal marrow after exposure.

Replacement or transplantation of marrow from another individual is termed "homografting." In man or in animals, in order to produce a successful homograft, the recipient's immune response must first be paralyzed. This is fairly easily accomplished in lower animals. In mice it is possible to administer 400 to 500 r. total body radiation, and then successfully transplant marrow from another animal or even from another species. In higher animals, however, this becomes much more difficult. A recent discouraging report described chimpanzees given total body radiation of about 1200 to 1400 r.[1] Despite the use of very large bone marrow transplants (actually the whole marrows from other chimpanzees), no evidence whatsoever of a marrow homograft was detected. Since the chimpanzee is a primate close to man, one must wonder whether this may be also true in human beings.

Bone marrow for possible marrow transplants is obtained by aspirating from multiple donor sites, using a Vim-Silverman No. 14 needle. In the older child and adult the best source of marrow is the iliac crest; the sternum also provides good rich marrow. In small children, the tibia is a rich source of marrow. With multiple aspirations, it is possible to obtain between 10 and 20 billion nucleated cells from an adult.

The evidence for homografting in man is very controversial. Thomas and

associates[2, 3] have treated a fairly extensive series of patients suffering from leukemia using total body radiation, followed by various forms of bone marrow transplantations. They have secured only temporary marrow transplants in their cases.

One of the most widely publicized studies of bone marrow transplantation reported was that of Mathé and associates in Paris.[4] These investigators treated a number of Yugoslavian atomic scientists who were accidentally exposed to large doses of total body radiation (200 to 900 r.) in a nuclear reactor accident. The victims arrived in Paris about one month after being exposed. At this point, Mathé transfused them with large amounts of marrow from normal donors. In several instances, hematologic changes were seen which Mathé interpreted as brief but definite evidence of temporary functioning of the bone marrow transplants. He believes strongly that this transplanted bone marrow function tided the patients over until their own bone marrow was again able to function. Other authorities have questioned these results. Beilby[5] has recently reported what seems to be the first definite instance of "permanent" homograft of bone marrow in man. His patient was a 30 year old woman with Hodgkin's disease treated serially with x-ray, corticosteroids, and large doses of chlorambucil. A successful transplantation of bone marrow from her sister who is not an identical twin has been documented for more than nine months.

However, even if homograft is possible in man, the use of radiation as treatment in acute leukemia is another problem. Is leukemia itself sensitive to irradiation? It has long been taught that the more rapidly a cell is dividing, the more sensitive it is to ionizing radiation. This probably is not the case in acute leukemia. Burchenal et al.[6] have shown that mouse leukemia is not "sterilized" by 1000 r. One of Thomas and associates' more recent cases with acute leukemia was a child who was an identical twin.[7] This child was treated with 1200 r. of total body irradiation, followed by a transplant of her normal twin's bone marrow. She survived the irradiation well and the graft from her identical twin was successful. However, she died only a few months later of leukemia. Therefore, it seems that, at least in the feasible dosage of up to 1200 to 1400 r., acute leukemia of childhood will survive total body irradiation. However, the lack of uniformity of administering the radiation may also have played a role in the unsuccessful results of these investigations. There are now three radiation units in the United States which will provide nearly uniform exposure of the whole body. These are at the Institute of Nuclear Research, Oak Ridge, Tennessee, the City of Hope, Duarte, California, and at our institution. Research from these centers will undoubtedly resolve this technical point.

Even though this form of therapy cannot be considered a cure for leukemia, there may be a place for it on an experimental basis. For example,

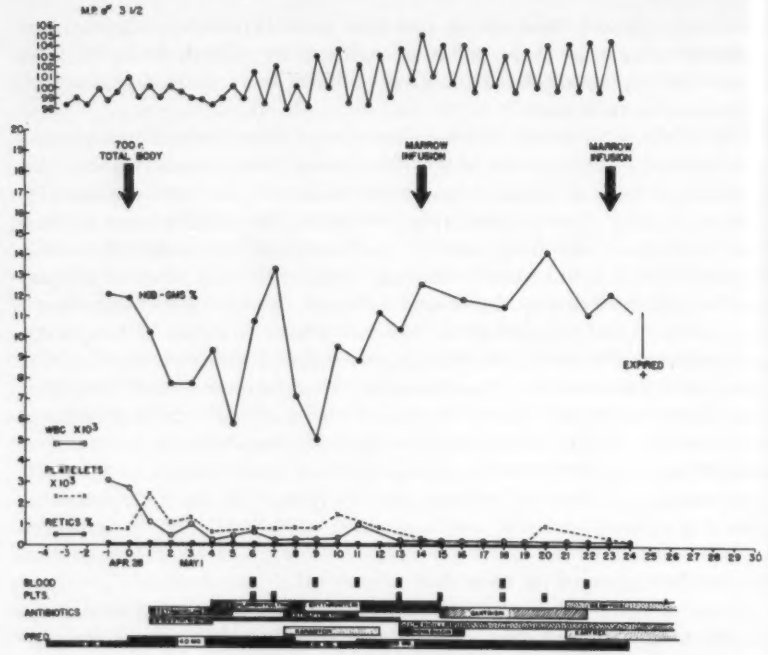

FIG. 2. Terminal clinical course of a child with acute leukemia who received repeated bone marrow transfusions. Note the lack of peripheral blood response.

if a child with acute leukemia is refractory to conventional chemotherapy and is in terminal leukemic relapse, the possibility of using total body irradiation may be considered. In this instance total body irradiation may be used as another modality to attain temporary remission. This plan has been followed by Andrews at Oak Ridge.[8] He has treated a number of leukemic children with 200 to 400 r. of total body irradiation and attained definite although short-lived remissions. These remissions are comparable to those obtained with conventional chemotherapeutic agents.

Our experience with this form of treatment may be illustrated by the case of a child in a terminal leukemic relapse who had had a 9½ month remission on standard forms of therapy (fig. 2). His white blood cell count was 2,500 per cu. mm. and his platelet count 10,000. He was placed in the total body irradiator and given a body dose of 700 r. Despite this very large dose given over a 30 minute period of time, he had few of the acute gastrointestinal symptoms which are commonly thought to be associated with acute radiation injury. He was brought to a special room where

elaborate and strict isolation precautions were maintained. Whole blood transfusions were given at times of extreme hemorrhage. He was transfused with 10 billion nucleated cells obtained from a normal donor. Despite this, there was no change in his peripheral response. Shortly before his death, approximately 50 billion nucleated cells were obtained by sterile post-mortem technique from a cadaver. This was injected intravenously. Again no response whatsoever of the peripheral blood count was observed. This unfortunately is similar to the experience of almost everyone who has used homografts in human beings.

In a third and final group of patients, total body irradiation may have the most profitable and encouraging results. These patients have widespread malignancy but an intact bone marrow. It is possible to use autologous (patient's own) marrow to protect against hematopoietic depression from large doses of radiation or chemotherapeutic agents. In the same line, early in the course of many tumors of childhood, the bone marrow and hematopoietic system may not be invaded. Theoretically, at least in these cases, if bone marrow could be removed early in the course of the disease and preserved in a suitable fashion, it would then be available near the end of the course when the bone marrow is depleted.

In a recent case we have combined autologous marrow therapy with total body irradiation to treat a child with severe central nervous system leukemic involvement, although the marrow was in remission. This resulted in complete amelioration of the neurologic complications and the child is still well five months after radiation. Severe hematologic depression lasted only two weeks.

If current research in preservation of bone marrow by glycerol freezing or similar techniques is successful, one can anticipate that marrow may be taken early in the course of childhood malignancy. Later, this marrow can be used to counteract the hematopoietic depression of chemotherapeutic or radiologic therapies.

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SYMPOSIUM: DIAGNOSIS AND TREATMENT OF BLADDER NECK OBSTRUCTION

W. Dabney Jarman, M.D.*
Timothy Kelly, M.D.†
Leonard B. Berman, M.D.‡

Dr. Jarman:

Bladder neck obstruction, as such, can be either congenital or neurogenic in origin. This discussion is concerned with the congenital type.

The types of mechanical obstruction at the bladder neck seen in children may be due either to congenital prostatic valve in the male, congenital hypertrophy of the verumontanum, congenital hypertrophy of the internal sphincteric area, or fibrous band congenital constriction. The signs and symptoms associated with bladder neck obstruction in children vary considerably. The most common is infection. In the series of cases to be reported by Dr. Berman, 79 per cent of children with obstruction had infection and approximately 85 per cent showed the severe form manifested by chills and fever. This statement might be emphasized by saying that infection is usually a complication of obstruction, whether in a child or an adult; frequently it is a late one. In addition to infection, common clinical features include straining on urination, enuresis, urgency, overflow incontinence, retention, and at times hematuria.

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If enuresis persists beyond 4 years of age, it is felt that the child should be studied for question of obstruction. In a fairly large group of enuretic children studied,[1] 28 per cent above the age of 4 years showed obstructions of one form or another. Therefore, it would be well to remember that any obstructive lesion at the bladder neck or urethra, with or without infection, can produce vesical irritability.

The diagnosis of obstruction of the lower urinary tract of children is usually arrived at by excretory urography, retrograde cystography, cystourethroscopic examination, retrograde cystoscopic examinations with pyelograms, and straight cystoscopy. The excretory urogram in the child will give an estimate of renal function and also frequently will indicate whether there are anomalies to consider, obstruction in the lower urinary tract or the results of obstruction in the upper urinary tract.

It is not difficult to make the diagnosis of bladder neck obstruction when the condition is well advanced; late manifestations include trabeculation of the bladder with cellule formation, ureteral reflux noted on cystogram, reduplicated mucosal folds at the bladder neck, a tight urethra or, in the male, definite valves or hypertrophy of the verumontanum. In the female, evidence of obstruction in the bladder can be identical with that in the male, depending entirely on the degree of obstruction and its duration.

The treatment of bladder neck obstruction in boys is surgical; it is dangerous and futile to attempt dilatation. Depending on the experience of the surgeon a transurethral or open surgical route may be used. Most urologists agree that in small boys, where instrumentation is difficult due to the size of the urethra, open surgery is the ideal choice.

In girls the indications for institution of surgical treatment are sometimes difficult to establish. Most urologists who have been observing this problem for many years feel that there are many children who fall into a so-called borderline group. There are those who feel that in this borderline group repeated dilatation may be the answer; they advise trying dilatation with instruments as large as 26 to 30 French before offering open surgical corrective measures.

Quoting Nesbit and Baum:[2] "A plea is made for physicians to include in their instructions to the parents of newborn children information regarding the need for observance of micturitional behavior. When this is not normal, an early investigation should be advised."

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Dr. Kelly:

Bladder neck obstruction in children is becoming recognized with such increasing frequency that it can be safely said to be the commonest obstructive lesion encountered in pediatric practice. According to most urologists about 75 per cent of the patients are girls. Table 1 shows the age and sex incidence in a series of 100 cases in the Washington, D. C. area recently reviewed.

The children who develop infection will usually have more outstanding complaints; these may be said to be luckier children in that the diagnosis will be established more rapidly. Infection, however, may be a late manifestation. These youngsters may have large dilated bladders and far advanced upper urinary tract changes without having had any evidence of infection either by clinical history or by laboratory examination preceding the diagnosis or at the time the diagnosis is established.

In addition to frequency of urination, straining on urination, and slow stream, the usual symptoms of obstruction, a very important one is infrequency of urination. The youngster who can go for a long trip in the car and never have to stop to go to the bathroom may be showing an equally important and major symptom.

The presence of vesical ureteral reflux on retrograde cystography in the absence of neurogenic disease is one of the manifestations of prolonged increased intravesical pressure. Most urologists feel that this is never a normal phenomenon, but always a manifestation of lower urinary tract obstruction and of more advanced disease. The youngsters who demonstrate reflux up into the ureters and renal pelves from the bladder have had some destruction of the normal mechanisms which contain urine in the bladder; this is one of the factors which make treatment more urgent.

It is important to realize that there may be no abnormalities visualized

TABLE 1

Age and Sex Incidence in Series of 100 Cases Reviewed

Age	Per Cent of Patients
10 years or older	25
Under 10 years	75
Range: Newborn to 17 years	
Sex	**Per Cent of Patients**
Female	66
Male	33

TABLE 2

Types of Surgery

Suprapubic: 35 patients	
Posterior wedge resection	
Bradford-Young resection	
Lateral and posterior bladder neck resection	
Transurethral Resection: 3 patients (12 years or older)	

by intravenous pyelography and the child yet have a very significant bladder neck obstruction. The bladder may be normal in size and there may be no residual urine on the postvoiding film, but this means only that the upper and lower tracts have not reached the stage of decompensation.

There are several types of bladder neck contracture as visualized at cystoscopy: valves or mucosal folds are probably the least common; the most common is a constricting ring of tissue which may be either muscular hypertrophy or fibrous contracture of the bladder neck. These cannot be differentiated endoscopically but must be determined by the pathologist. The obstruction may be concentric, it may form a median bar on the posterior lip of the bladder, or in some cases there is a so-called "lateral pillar" type of obstruction where there are two bands of tissue narrowing the lumen of the bladder neck in an anterior-posterior direction.

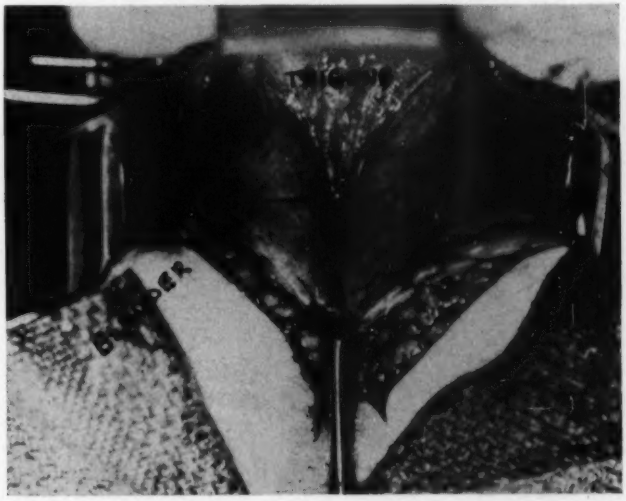

FIG. 1. Open bladder at surgery before transvesical removal of a bladder neck contracture.

In the bladder, the most striking change is trabeculation, a manifestation of hypertrophy of the detrusor muscle. Except in neurogenic bladders, trabeculation always means obstruction. Many of these youngsters will have large bladders; in the literature there is increasing use of the term "megacystis" to describe bladders which have decompensated and become much larger than their usual size. The appearance of the ureteral orifice varies; dilated orifices lead to vesical ureteral reflux.

Treatment of this abnormality falls into one of several categories: medication, dilatation or surgery. The only medication indicated is treatment for the infection; the drugs which increase smooth muscle tone have no place in treatment, except possibly postoperatively. It is sometimes a difficult decision to decide when to dilate and when to operate. Bladder neck obstruction warrants correction not only because of what has happened but also because of what might happen. A larger number of children fail to respond to dilatation, and in the process of this failure have had repeated insults either by pressure or by infection to the upper urinary tract to the point where they develop a well established urinary

FIG. 2. Open bladder at surgery after transvesical removal of a bladder neck contracture.

tract infection which subsequent surgical correction does not cure. However, the fact that the infection is not cured immediately or for a long period of time after the operation does not nullify the value of the operation. If the obstruction is relieved, the back pressure has also been corrected; this will substantially aid further medical treatment of infection.

Table 2 demonstrates the types of surgery carried out in a group of 35 patients. Simple removal of the posterior lip of the bladder neck seems to be enough in many instances. The Bradford-Young operation is satisfactory for most. This is removal of the posterior lip of the bladder neck and reconstruction of the anterior bladder neck. Removal of the lateral and posterior bladder neck is a further extension; transurethral resection is reserved for older children because of the higher incidence of secondary urethral or bladder neck strictures when the transurethral route is used in younger children.

Figure 1 shows the open bladder at surgery (transvesical procedure) and the contracture. Figure 2 shows the bladder neck after the tissue has been removed.

The results with these various operative procedures for bladder neck obstruction generally are good. There are some failures as far as persistence of infection, but in most children there is a resolution of the reflux, decrease in bladder size, and rapid clearing of infection. In addition to this, there are other nonspecific changes observed; abdominal pains disappear, the appetite increases, and generally the weight gain and increased thriving which occur are outstanding.

Dr. Berman:

The urologic literature contains large numbers of cases of bladder neck obstruction. In a 10 year review which Drs. Crotty and Tina of this hospital have carried out, there were 600 to 700 reported cases of bladder neck obstruction; it, therefore, must be a common disease. However, when they examined the records at this hospital they were able to discover only the following numbers of cases: In 1955, 1956 and 1957, there were respectively one, two and five diagnoses of bladder neck obstruction. In 1958, when aggressive case finding began, the incidence increased to 14, and in 1959, to over 35.

Bladder neck obstruction is indeed an easy diagnosis to make. The symptoms fall into two categories: those due to mechanical obstruction and those due to the infection. If however, this is such an easy diagnosis, why are patients being missed? There are probably three reasons: 1) The house staff and the community of pediatricians in this hospital have not in the past automatically considered bladder neck obstruction as a possi-

bility when dealing with a child with pyuria. As an example, there is a published series of 18 children with pyuria who were investigated in whom 18 bladder neck obstructions were found. This seems extraordinary, but it duplicates exactly the experience of the renal laboratory here; in a retrospective examination of fifteen of our own cases of pyuria, there were bladder neck obstructions in all. 2) The right questions are not asked in the history; for example, questions about the pattern of the child's urination. Most mothers will not volunteer information of significance, i.e., does the child fail to urinate when he gets up in the morning, or does he go without voiding for several hours during the day? 3) Varying interpretation of intravenous pyelograms. If the diagnosis is suspected and an intravenous pyelogram with postvoiding film is done, the problem of residual urine and its interpretation is encountered. There are those who consider a certain per cent of residual urine to be normal; there are others who insist that any discernable amount of dye in the postvoiding film is abnormal. Our own studies demonstrate that residual urine must always be investigated for the possibility of an associated bladder neck obstruction.

Regardless of the method of correcting the bladder neck obstruction, it is quite striking how often the infection persists and becomes chronic. Infection, when well established anywhere in the genitourinary tract, bladder, ureters, or kidney parenchyma, no longer needs for its perpetuation the mechanical factors which initiated the infection. Correcting the bladder neck has, in our small postoperative experience, certainly not been a panacea. It does protect against further mechanical damage but it does not insure freedom from persistent infection. It is unfortunate that the association of obstructive uropathy with older age groups has led to the supposition that its appearance in childhood is rare.

The Place of the Pediatrician in Children's Eye Problems*

MARSHALL M. PARKS, M.D.†

The physician who accepts responsibility for the over-all medical care of infants and children finds that a high proportion of the everyday problems he encounters are of an ophthalmological nature. Many are beyond his scope of interest and proficiency of treatment, and he does well to refer such cases to the ophthalmologist. However, there remains a sizeable group which should be handled with confidence by the physician who happens not to be an eye specialist. Moreover, most parents expect the physician who cares for the general medical problems of their child to treat the minor eye disturbances, and they generally have confidence in his treatment. Occasionally a parent will err in considering a serious eye case as being minor, but an alert physician can forthrightly correct this mistake and the patient is none the worse for it.

Although this presentation is orientated toward discussing those eye cases which are treated safely by the pediatrician, there are certain types of cases which are not. These disorders are classified into the following five groups: 1) conspicuous congenital defects, 2) sight problems, 3) neoplasms, such as retinoblastoma and hemangiomata, 4) serious inflammations, such as orbital cellulitis, and 5) serious injuries, such as lacerated cornea. Examples of conspicuous congenital defects are ptosis, strabismus, infantile glaucoma, and cataracts.

The pediatrician may become aware of a sight problem by noting a) signs that the vision is poor, illustrated by the child who strains to see or holds things closely to his eyes, b) symptoms that the vision is poor, illustrated by the child who is unable to see material on the blackboard or who has visual discomfort associated with the use of his eyes, and c) findings elicited by visual screening. Visual acuity less than 20/20 in children over 7 years of age and less than 20/30 in those under 7 years of age is considered defective.

The eye problems which the pediatrician should feel confident to treat are 1) minor injuries, 2) minor inflammations, and 3) minor congenital defects. The volume of these minor conditions is much larger than their major counterparts. The physician who is not an ophthalmologist usually

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is the first to see them, must differentiate them from the more serious ones, and usually follow through with the treatment. The following is an ophthalmologist's point of view on how the pediatrician should manage the more common of these minor eye problems.

A common minor injury is subconjunctival hemorrhage. Its usual cause is a slight blow to the eye, or increased venous pressure from staining or coughing. The eye must be carefully inspected to ascertain that there is no deeper damage. The parents are assured that it will spontaneously absorb over a period of 5 to 10 days.

Care must be taken to make sure that subconjunctival hemorrhage is not associated with bleeding into the anterior chamber. No matter how insignificant the original hyphemia may be, all ophthalmologists fear and respect secondary hemorrhaging which has the potential for destroying the eye. Therefore, hyphemia is "too hot a potato" to be retained in the hands of the pediatrician. This is one particular injury in which parents frequently err in considering minor. The pediatrician renders a great service in promptly correcting any such misconception.

Corneal abrasion is a painful injury which can be disturbing to the patient's family because the injured child usually becomes somnolent. This must be nature's way of easing the pain and aiding the healing. The injured eye is usually sensitive to light, and there is blepharospasm, tearing, and injection of the conjunctiva. The abrasion is seen as roughening of the normally smooth transparent cornea. The diagnosis is assured by observing the green discoloration of the abraded epithelial area after 2 per cent sodium fluorescein has been instilled. The intact corneal epithelium does not accept the stain.

The greatest relief from the pain is obtained by applying a tight dressing which completely immobilizes the lid. The bandage also assists the healing process by preventing the opening and closure of the blepharospastic lid and rubbing of the eye, both of which tend to dislodge the tenuously attached newly regenerated epithelial cell. No ointment should be instilled because lubricant makes it difficult for the new epithelial cell to adhere to the wound base. No topical anesthesia should be instilled because it inhibits epithelialization. No topical antibiotics need be instilled because the tears possess an antibacterial substance known as lysozyme, and, furthermore, if rapid healing is achieved, there is no reason to fear infection. Therefore, a simple, properly applied dry dressing, left undisturbed for 24 hours is the best treatment. Aspirin is useful to control any discomfort which is not fully relieved by the bandage. Healing of all but the most extensive abrasions is usually complete within 24 hours if the above regimen is followed. However, if there is residual stain acceptance, the same treatment should be continued for another 24 hours or until the cornea accepts no stain.

Lacerations about the lids are handled in the same manner as any skin laceration with two exceptions: lacerations through the canaliculus and across the lash line of the lid. Each deserves special handling by the ophthalmologist. In addition, an edematous, ecchymotic lacerated lid should not be repaired without first separating the lids and inspecting the eye for damage.

A foreign body adherent to, or embedded in, corneal or conjunctival tissue can usually be dislodged with a jet-stream of water forced through a small needle on a syringe. A topical anesthetic should be instilled prior to attempting this maneuver. If this method fails, touch the tip of the needle to the foreign body. Be aware of the possibility that the embedded metallic foreign body may undergo oxidation and result in deposition of pigment in surrounding corneal tissue. It is easy to mistake the foreign body removal as incomplete due to this rust spot. An ophthalmologist may burr away the rust spot but the pediatrician should not attempt it. After a corneal foreign body removal has been completed and fluorescein dye is accepted by the site previously occupied by the foreign body, the treatment from this point is identical to that of corneal abrasion.

Of the minor inflammations, conjunctivitis is the most frequent. Conjunctivitis results from four principal causes: 1) physical, 2) chemical, 3) infectious, and 4) allergic.

The physical factor causing conjunctivitis is often an inert foreign particle in the conjunctival sac; for example, sand or a gnat. The treatment is removal, which is best accomplished by wiping, twisting, or spinning a dry cotton applicator over the foreign particle after having previously instilled a topical anesthetic. The foreign body incites the conjunctiva to put out mucus which surrounds it, and the spinning dry cotton applicator entwines the mucus which carries the foreign body with it. The lids may have to be everted in order to see the foreign material.

Chemical conjunctivitis may have a dramatic onset due to a toxic substance accidentally being instilled into the eyes. This emergency should be treated with copious irrigation of water into the conjunctival sac. The child's eyelids should be held apart while body temperature tap water is flushed into the eye for several seconds. These should be the first instructions given to a frantic parent telephoning for instructions about emergency treatment. After the irrigation, when more objective thought and observations are possible, many emergencies prove to be less serious than originally feared. The criteria as to whether further care by an ophthalmologist is warranted are persistence of pain, tearing, photosensitivity, and blepharospasm one hour after the injury. However, certain alkaline substances present a special problem. For example, lime and the liquid center of a golf ball adhere by burning into the moist tissue, producing progressive

serious inflammations and scarring. From the moment of injury it is obvious that this is a problem for the ophthalmologist.

A less dramatic type of transient chemical conjunctivitis is that caused by chlorine in a swimming pool. In reply to a request for medication to prevent or alleviate this, the parents should be instructed that the conjunctivitis is less uncomfortable and less dangerous than the medication.

A third type of conjunctivitis is infectious in nature, either viral or bacterial. The typical acute "pink eye" is localized to the conjunctiva, causing maximal congestion in the fornices and a purulent discharge which causes the lids to mat together upon awakening. A viral conjunctivitis may be associated with systemic findings, such as rhinorrhea, respiratory symptoms, adenopathy, and fever. There may be lymphocytosis and leukopenia. A topical antibiotic shortens the course of the bacterial disease and aids in preventing the complications of styes and chalazions. The recurrence rate is lessened if treatment is continued for two or three days after the conjunctivitis appears cured.

One particular viral conjunctivitis which is very productive of purulent material, much congestion, and occasionally bleeding of the conjunctiva is inclusion blennorrhea of the newborn. An agent, presumably a virus, causes inclusion bodies to form in the conjunctival epithelial cells. It is transmitted to the infant's conjunctiva from the mother's birth canal, and signs of the infection appear five days later. It responds specifically to sodium sulfacetamide.

The clinician must realize that a large percentage of the conjunctivitides are due to allergy. Pollen is the most common allergen, but animal fur, wool and feathers also must be kept in mind. Allergic conjunctivitis due to pollen is characterized by itchy red eyes, the redness being confined to the bulbar conjunctiva presenting between the lids, a ropy discharge, and a pale "bumpy" conjunctiva on the inner side of the lids due to eosinophilic papules. Sometimes the conjunctivitis is limited to one sector on one eye adjacent to the limbus. The condition is worse at the end of the day due to the prolonged time pollen has contacted the eye, and is improved upon awakening. Instillation of a topical corticosteroid four times daily affords dramatic relief. The medication should be discontinued after one week in order to determine if the allergen is still prevalent. If the symptoms return, the same regimen should be restarted for another week. Therapy with a systemic antihistamine is not as effective as topical corticosteroid; however, if there are associated rhinorrhea, nasal congestion, sneezing, and itchy nose, the antihistamine alleviates these symptoms.

Other minor inflammations seen in great volume among children are styes, chalazions, and granulated eyelids. Hot compresses tend to localize the stye and encourage rupture and drainage. During the acute period when

the lid is tender, an antibiotic can be instilled into the conjunctival sac, but as soon as the tenderness subsides the ointment should be massaged along the lash margins of the lids in an attempt to work the antibiotic into the eyelash roots where the staphylococci are thriving. This should be carried on for one week in order to prevent new styes.

The bacteria causing the stye may ascend from the eyelash roots up ducts which empty oil from glands deep in the lid tissue, causing a chalazion. The infection may evolve into a chronic cyst easily visible on the conjunctival side of the everted lid; more infrequently an acute abscess of the lid will develop. In either event the treatment is surgical and outside the pediatrician's responsibility.

Granulated lids are a seborrheic condition along lash margins. The *Pityrosporum ovale* organism seems to prefer blond children. These organisms destroy the vital contents of the epithelial cells and the dead remains are cast off as granules. Usually there is a minimal inflammatory response which accounts for the injected lid margins. Nightly massage of yellow oxide of mercury into the lash margins of the lids controls it, but there is no permanent cure for this annoying little disturbance.

Those who deal with infants well know of the frequent occurrence of congenital impatency of the nasolacrimal ducts. The classical appearance is the "wet eye" due to tears spilling over the lower lids, associated with a mucopurulent exudate due to infection. Often the tear sac becomes distended with the mucopurulent material which is easily evacuated through the canaliculi into the conjunctival sac by pressing the sac against the underlying bony anatomy. Fortunately, the majority spontaneously establish patency prior to 3 months of age. Until this happens it is wise to have the parent compress the tear sac with the index finger four times per day. This is painless and prevents the development of hydrops of the tear sac. A combined antibiotic and corticosteroid medication should be instilled in the eye following the tear sac compression. This helps control the infection and decreases the inflammatory edema of the nasolacrimal epithelial lining, thereby allowing the largest possible calibre of opening within the nasolacrimal system, if any is present. If the impatency does not spontaneously open within the first three months, the chances become increasingly poor that it will do so in the future. Therefore, probing of the "blocked" system should be considered after 3 months of age. This may be accomplished as an office procedure, using only topical anesthesia until 6 to 8 months of age, but general anesthesia is required to manage the older children.

SUMMARY

The pediatrician has a large role in the management of eye problems among children. His knowledge and attitude about handling these problems

determine to a great extent the standard of eye care for children in his community.

The specific minor injuries, inflammations, and congenital defects the pediatrician is expected to treat are discussed from an ophthalmologist's point of view.

The Editor's Column

Hunting in Season

As summer arrives, bringing with it school vacations, swimming, and sunshine, it also brings health hazards to children. Many of these hazards are obvious, such as sunburn and fractures, but others must be sought for. One of these occult dangers is acute lead encephalopathy which has its peak incidence (over 80 per cent) between May and October. This increase may be due to greater solar irradiation to the skin which in turn produces more vitamin D which (probably) facilitates absorption of lead from the gut. In addition, infection occurring in the summer is more likely to cause dehydration and acidosis, factors which mobilize lead from depots in bone.

When a child of pre-school age convulses, with or without fever, during this season, the differential diagnosis must include plumbism. Since there are no characteristic physical or cerebrospinal fluid abnormalities, blood lead levels must be determined in any such child with a history of pica for lead containing substances (paint, plaster, putty, or newspaper), anemia, stippled red blood cells, or "lead lines" on x-ray. In order to prevent brain damage or death, treatment with calcium disodium ethylenediaminetetraacetate (EDTA) must be started early. It is essential, therefore, that these cases be hunted for, that all convulsions be considered symptomatic of serious disease until proven otherwise, and that questioning about pica be included in every history.

GEORGE J. COHEN, M.D.

Book Reviews

Resuscitation of the Newborn Infant: Principles and Practice. Edited by HAROLD ABRAMSON, M.D., 274 pages, illustrated, St. Louis: The C. V. Mosby Company, 1960, $10.00.

This book is an outgrowth of a report on the resuscitation of newborn infants by the Special Committee on Infant Mortality of the Medical Society of the County of New York. Its 17 chapters (by 24 contributors, many of whom are well known in their respective fields) attempt to ". . . thoroughly consider the theoretical and factual aspects of the problem in relation to practical bedside application."

This, embodying, as it does, the respective talents of the physiologist, pathologist, obstetrician, anesthesiologist and pediatrician, is in keeping with the modern medical approach of utilizing knowledge from many professional fields in an onslaught on a particularly thorny problem. It is, therefore, particularly regrettable and a little puzzling that the book doesn't quite come off.

Part of this may be due to the quite differing styles of presentation of material by the authors of the various chapters (who curiously are not identified). Thus, chapters on the etiology of perinatal disability and mechanical resuscitators are little more than outlines; on the other hand, the chapter on physiology and biochemistry is much more completely written but suffers badly from lack of a summary (as do the majority of the sections).

The sections on the history and physical examination of the mother, the two chapters concerning the pediatric examination (in the delivery room and in the nursery) and the section on laboratory procedures are so sketchy that this reviewer would feel more comfortable consulting standard textbooks. Portions of additional chapters on pathology, and diagnosis of fetal distress are completely confusing—one wonders what the authors' aims were. On the other hand, the section on resuscitation procedures, *per se*, is quite informative and probably the book's most valuable. The section on infant mortality presents useful data; there is a glossary which also adds to the book's value.

Illustrations and tables are well reproduced but suffer from insufficient headings; this seriously detracts from their value. Conversely, perhaps the book's strongest point is the large number of references at the end of each chapter. Perhaps the editor's intent was to present data in outline form and stimulate further reading—he does not so state in the preface.

This book is disappointing. To achieve the "comprehensive" approach would probably require twice as many pages. It is unfortunate that the editors felt the need to be so concise.

J. WILLIAM OBERMAN, M.D

Instructional Course Lectures, Volume XVII (The American Academy of Orthopaedic Surgeons). Edited by FRED C. REYNOLDS, M.D., 421 pages, illustrated, St. Louis: The C. V. Mosby Company, 1960, $18.50.

The 1960 Volume of the Instructional Course Series of The American Academy of Orthopaedic Surgeons should be of interest to the general surgeon caring for fractures and athletic injuries, as well as to the orthopedic surgeon. The entire volume is well illustrated, which provides for easy reading and a ready reference. The various subjects covered are evidently prepared by men chosen for their wide clinical experience as well as their teaching ability.

The section on fractures of the elbow in children includes not only the early treatment but the latent complications arising from fractures about the elbow. The diagnosis and care of arterial injury in the extremities reflects the desirability of the surgeon, general or orthopedic, working closely with the vascular surgeon.

The symposium on the management of fresh fractures of the neck of the femur is a good summary of the present-day approach to this ever-present difficult problem. The advantages and disadvantages of the use of the prosthesis in the fresh fractures of the femoral neck are well covered. The orthopedic surgeon concerned with the reconstruction of nonunion of fractures will benefit from the well prepared and presented section on bone grafts.

Part III is given over to children's orthopedics, with particular reference to long-bone growth and the treatment of unequal leg lengths. The highly specialized care of the child amputee is well handled.

The section on disability evaluations will be helpful to those dealing with compensation and liability cases. All physicians caring for athletic injuries will be interested in the symposium on this subject.

While not designed as a textbook, the 1960 volume, combined with the previous volumes, is a valuable addition to the library of both the general and the orthopedic surgeon.

WILLIAM J. TOBIN, M.D.

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